

# COGNITIVE EFFECTS OF ALCOHOL AND BENZODIAZEPINES

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# Substance Related Brain Injury: Basic Research Findings

- All neurotoxic substances have an acute intoxicating effect (and withdrawal effect) that produces changes in cognition, usually in the areas of attention, memory and executive function
- All substances have the potential to produce an acute brain injury, generally related to overintoxication (overdoses) and its secondary effects (hypoxia etc)

# Substance Related Brain Injury: Basic Research Findings

- Most substances (if not all) will produce an acquired brain injury in the long term
- There is a consistent theme in the drug and alcohol literature that initial research into a substance suggests that there is no brain injury from the substance, but years later this is shown to be not true
- The chronic brain syndrome often is more extensive than the acute syndrome

# ALCOHOL RELATED BRAIN INJURY

# ALCOHOL RELATED BRAIN INJURY

- Physical injury to the brain sustained as a result of heavy alcohol consumption
- Affects people in two ways
  - Thinking, emotion and behaviour
  - Physical movement
- It is not the same as having an intellectual disability nor a dementia

# WERNICKE-KORSAKOFF SYNDROME

- Caused by thiamine deficiency
- Neuropathology
  - Mamillary bodies
  - Thalamus
  - Hypothalamus
  - Brain stem
  - Cerebellum
  - Frontal lobe atrophy

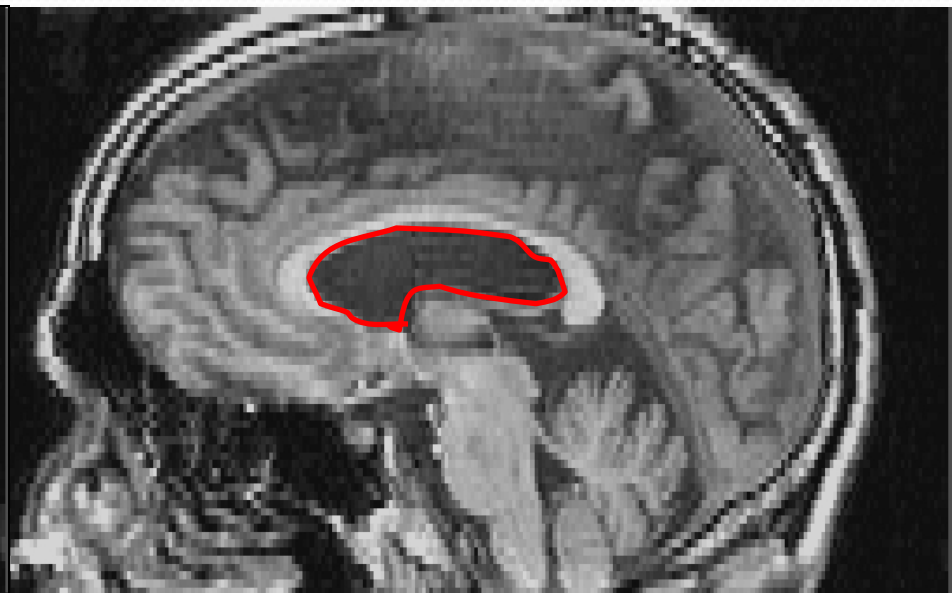
# WERNICKE-KORSAKOFF SYNDROME

- Main features are:
  - ataxia - poor balance, inco-ordination
  - paralysis of eye movements
  - confusion

# EtOH Shrinkage of the Ventricles



**Non-alcoholic**



**Alcoholic**

# EtOH Shrinkage of the Cerebellum



**Healthy Control**



**Alcoholic**

# MAJOR MEDICAL COMPLICATIONS

(presented as percentages - young/old)

- Cerebellar ataxia 14/46
- Peripheral neuropathy 11/42
- Head Injury 21/22
- Liver disease 10/22
- Other neurological disorders 13/18
- Seizures 13/14
- Korsakoff's Psychosis 0/10
- Wernicke's encephalopathy 2/5
- Dementia 0/5

# TWO ALCOHOL RELATED BRAIN INJURY SYNDROMES

- Memory impairment
- Executive dysfunction

# MAIN FEATURES OF THE AMNESIC SYNDROME

- Immediate memory is not affected
- Difficulty remembering recent events or recently learned information
- Achronogenesis - loss of time tags
- Retrieving information stored in memory
- Confabulation - a tendency to make up memories
- Preserved learned behaviour

# THE DYSEXECUTIVE SYNDROME (ALCOHOLIC DEMENTIA)

- Thought to be caused by the neurotoxic effects of alcohol
- Cortical and subcortical atrophy is common
- Frontal lobe structures are particularly vulnerable and shrinkage is largely due to loss of white matter
- MRI and PET scans show specific regions of the cerebral cortex (superior frontal association cortex), hypothalamus and cerebellum, but not the basal ganglia
- Recovery may lead to partial reversal of CNS deficits and cognitive deficits
- Many of the regions that are normal in uncomplicated alcoholics are damaged in WKS (basal ganglia etc)

# Other Neuropathology

- Damage from alcohol and thiamine deficiency is seen in white matter loss, brain atrophy, selective loss of neurones in the superior frontal lobe and the basal ganglia
- However, it is not as simple as thiamine causes damage to some areas and alcohol to others
- There is evidence that there is an interaction effect between alcohol and thiamine deficiency in alcohol related brain damage, particularly in the white matter
- Damage to the cerebellum also appears to be multifactorial
- Patterns of damage appear to be related to lifetime alcohol consumption and to associated medical complications

# STEPS TO PROBLEM SOLVING

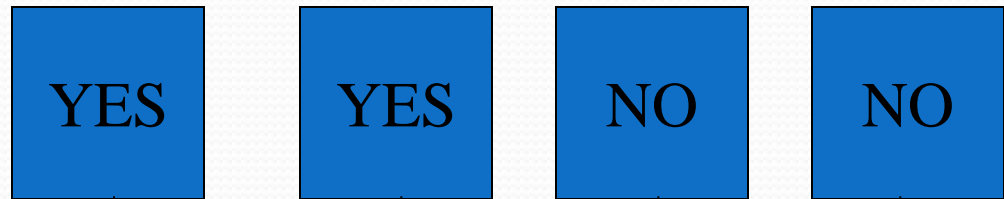
- Perceive incoming information
    - Form intentions
    - Create plans, programs
    - Inspect the performance
    - Regulate the behaviour
    - Verify conscious activity
  - Resultant behaviour or outcome
- 
- The diagram illustrates a feedback loop. A vertical line on the right side connects the 'Resultant behaviour or outcome' step back to the 'Perceive incoming information' step. A horizontal arrow points left from the top of this line to the 'Perceive incoming information' step. Another horizontal arrow points right from the bottom of this line to the 'Resultant behaviour or outcome' step. A small downward arrow is positioned below the 'Resultant behaviour or outcome' step.

# EXECUTIVE DYSFUNCTION

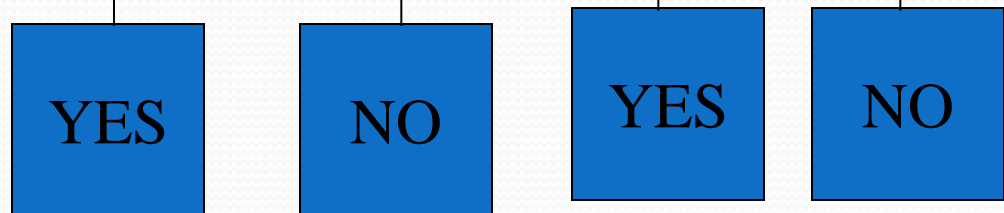
- Difficulties with:
  - Attention and concentration
  - Planning, organisation, problem solving
  - Complex, abstract and flexible thinking
  - Initiative
  - Emotional and behavioural change
  - Self awareness and insight

# Awareness and Insight

- Awareness



- Insight



# THINGS ARBI DOES NOT AFFECT

- Vocabulary and language
- Long term memory
- Any well learned skills
- Knowledge of facts and understanding of the world
- Knowledge of the social world
- ARBI is sometimes called the invisible disability because the person is still good at many things

# Research Issues

- Research in to the effects of alcohol on cognitive functioning have been plagued by methodological problems
- There appears to be an assumption of a linear relationship between alcohol use variables and cognitive problems
- Researchers continue to include in 'Alcoholics' groups people who have not drunk enough for long enough and then wonder why they don't find a relationship between drinking variables
- This raises doubts about the conclusions reached in a large number of studies, some which are often quoted as 'proof' of a position

# Drinking Patterns

- Safe levels of drinking for ARBI:
- Up to four drinks per day, no evidence of ARBI
- Between four and eight drinks per day, is a grey area
- Over eight drinks per day, high likelihood of ARBI
- Other issues:
  - Length of drinking history
  - Regular versus binge drinking
  - Age at which drinking commenced

# Adults and Substance Related Brain Injury

Assuming you are an adult and do not suffer an acute neurological event, those at risk of developing an ABI are:

- those who use a substance for at least ten years (if not fifteen)
- use above a particular threshold (eg over 4-8 standard drinks per day)
- are over the age of 40

# Adolescents and Drinking

- Recent studies have shown:
  - Those who first use before age 14 are at increased risk of developing alcohol use disorders
  - They are susceptible to blackouts, hangovers and alcoholic poisoning, are at elevated risk of neuro-degeneration (in regions of the brain responsible for new learning and memory), impairments in functional brain activity and neuro-cognitive deficits
  - There is evidence of decreased hippocampal volume
  - Heavy drinking erodes the development of transitional skills to adulthood
  - Binge drinking adolescents show poorer performance on problems solving tasks
  - However, these deficits seem resolvable with abstinence

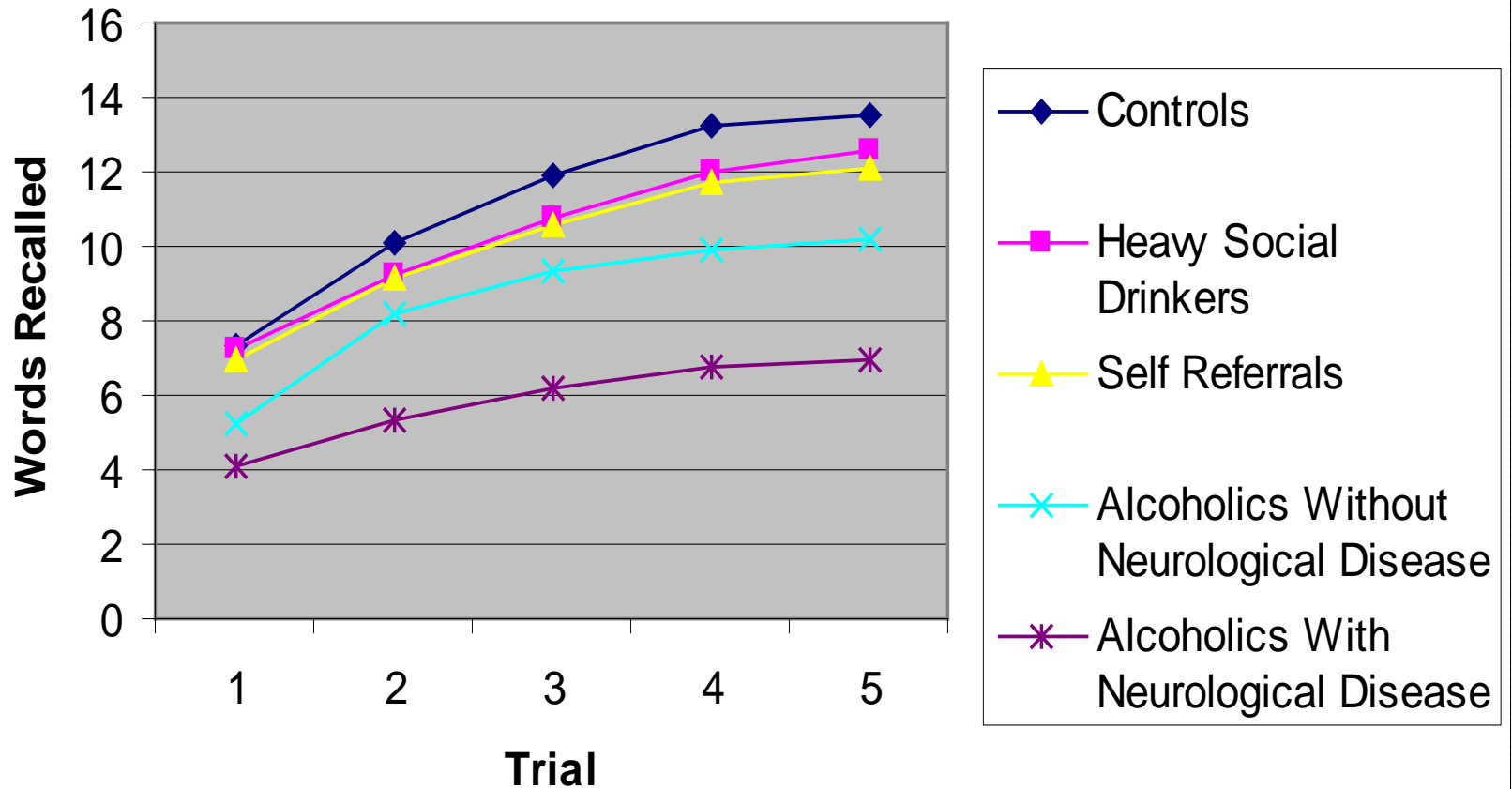
# Recovery

- Treatment of the W-KS with thiamine may lead to dramatic clinical improvement
- There will also be improvement (physically and cognitively) from the acute and withdrawal effects
- Some research has suggested full recovery with abstinence of two years or more
- However, quantitative MRI has shown that there is evidence of long term structural damage in abstinent alcoholics

# FACTORS RELATED TO RECOVERY

- No determination regarding the presence of a brain injury can be made until the effects of recent use or withdrawal are resolved
- Recovery from ARBI is related to
  - the severity of ARBI
  - the presence of neurological signs
  - the presence of other forms of acquired brain injury

## Performance of Social Drinkers and Alcoholics on the Rey Auditory Verbal Learning Test





# **BENZODIAZEPINES**

# Medical indications for use

- Anxiolytic – chronic/phobic anxiety and panic attacks
- Sedative and hypnotic – sleep disturbance and anaesthesia/pre-medication
- Anticonvulsant – status epilepticus, myoclonic and photic epilepsy
- Muscle relaxant – muscle spasm/spasticity
- Alcohol withdrawal



# Patterns of Use

- BZDs are one of the most prescribed drugs (4% of all prescriptions from General Practitioners)
- In Australia, BZDs are prescribed at the rate of six million PBS prescriptions (not including hospital and repatriation benefits) per year
- Up to 2% of the Australian adult population may be daily and long-term users of BZDs.
- Pharmaceutical records suggest that enough BZD is prescribed to enable 3% of the population to use every day (Cape et al., 2002, p.224).
- Over 40% of prescriptions given to people  $\geq 70$  years
- Night time use tends to increase with age
- 58% of current users report daily use for  $\geq 6$  months.

# Benzodiazepines

- Short term neurological effects
  - Act at limbic, thalamic and hypothalamic levels
  - Primary effects are anxiolytic, sedative, hypnotic, muscle relaxant and anticonvulsant
  - CNS effects are drowsiness, ataxia, fatigue, confusion, weakness and vertigo
- Short term cognitive effects
  - Anterograde amnesia is common and severity is dose dependent, memory for information presented under the influence is impaired
  - Reported cognitive problems with verbal fluency, psychomotor speed, reaction time, attention, episodic memory, semantic memory
  - No retrograde amnesia

# Adverse effects

- Cognitive impairment, decreased motor skills, daytime sedation
- Additive CNS depression (ethanol, antihistamines, opioids)
- Dependence
- Behavioural disinhibition (paradoxical)
- Anterograde amnesia
- Abrupt withdrawal can result in panic attacks, rebound anxiety
- Risk of foetal deformation (1st trimester)



# Benzos and Long-term Use

- Long-term use is common and associated with:
  - altered use patterns (from night time to daytime use)
  - excessive sedation
  - cognitive impairment
  - increased risk of accidents
  - adverse sleep effects
  - dependence and withdrawal (even at therapeutic doses)
- BZDs have an additive effect with alcohol / other CNS depressants, increasing the risk of harm
- BZDs have limited long-term efficacy.

# La Trobe University Research

- Following their introduction, the benzodiazepines quickly became the most widely used of all psychotropic drugs, with over a billion dollars worth sold each year (Lader & Petursson, 1983; Lucki & Rickels, 1986).
- Despite their obvious popularity, it took much longer for concerns to emerge that there may be long-term cognitive consequences of benzodiazepine use.
- Qualitative reviews of this literature (e.g. Barker et al., 2003; Stewart, 2005) indicate that the data are inconsistent, contradictory and difficult to interpret due to heterogeneity with respect to:
  - Psychiatric status
  - Use of other drugs and alcohol
  - Differing forms of the benzodiazepines
  - The range of doses used
  - Differing cognitive measures
  - Varying definitions of what “long term” means

# LTU Research program

- This program set out to determine:
- 1) Whether there are cognitive effects of long-term benzodiazepine use
- 2) Whether the cognitive function of long-term benzodiazepine users improved following withdrawal
- 3) Whether previous long-term benzodiazepine users were still impaired at follow-up as compared to controls or normative data
- 4) We then used the findings arising from the three previous meta-analyses to conduct an empirical study to investigate cognitive functioning in long-term benzodiazepine users who had withdrawn and remained abstinent for at least six months and compared these to two control groups, normals and a second group matched for levels of anxiety

# Are there cognitive effects of long-term benzodiazepine use?

- Moderate to large effect sizes were found for all cognitive domains, indicating that long term benzodiazepine users were significantly impaired in comparison to controls in all the areas assessed
- This indicates that the effects are global and not specific to any cognitive domain, but some domains (e.g. sensory processing, psychomotor speed, non-verbal memory and visuospatial processing) seem to be more severely affected than are the others

# Does the cognitive function of long-term benzodiazepine users improve following withdrawal?

- The results of study one clearly indicate that the residual deficit is associated with a long-term use of benzodiazepines, but these patients were still either using the agent or had only briefly (i.e. within days) withdrawn from them
- When compared to their initial assessment, previous long-term benzodiazepine users improved across all of the cognitive domains examined at the follow-up assessment.
- Visuospatial, attention/concentration, general intelligence, psychomotor speed and non-verbal memory significantly improved for benzodiazepine users when they discontinued.

## Are previous long-term benzodiazepine users still impaired at follow-up compared to controls or normative data?

- When compared to controls or norms, previous long-term benzodiazepine users performed more poorly across all cognitive categories, except sensory processing, when examined at follow-up assessment.
- Verbal memory, psychomotor speed, speed of processing, motor control/performance, visuospatial, general intelligence, attention/concentration and non-verbal memory) are all impaired.
- The results of this meta-analysis indicate that, compared to controls or norms, previous long-term benzodiazepine users performed more poorly across all cognitive categories, except sensory processing, when examined at follow-up assessment.

# Conclusion meta-analyses

- The results of the three meta-analyses support extreme caution in the use of long-term benzodiazepine therapy.
- Although these findings suggest that previous long-term benzodiazepine use may lead to impairments in cognition, some degree of improvement in cognitive function after withdrawal is observed.
- However, the data do not support a full recovery, at least in the first three months following cessation and suggest that there may be some permanent deficits or deficits that take periods longer than three months to recover.
- The aim of the last study was to determine whether there would be greater recovery with greater duration of abstinence and to control for the presence of anxiety and other medications

# Are previous long-term benzodiazepine users still impaired at follow-up compared to normal and anxious controls?

- Previous long term benzodiazepine users assessed after at least 6 months of abstinence continue to display cognitive deficits in a number of areas as compared to matched normal and anxious controls
- Significant moderate to large effects sizes were noted for
  - Verbal memory
  - Motor control/performance
  - Non-verbal memory
  - No effect for visuospatial skill, but strong trends
- Comparison of the effect sizes of the benzodiazepine versus the combined control groups and comparing these with the effect sizes emerging from the meta-analyses indicated consistent effect in the current study, although with larger effect sizes

# Overall conclusions

- Clear and consistent differences exist between the performance of long-term benzodiazepine users and those who do not use the drugs independent of their status with regard to anxiety
- The largest effects noted are in the domains of verbal memory and motor control/performance
- These functions are largely subserved by the hippocampal formation and the reticular formation amongst other regions
- The effect of long term benzodiazepine use is comparable to the levels of deficits noted with moderate to severe closed head injury
- This raises considerable concern about the clinical application for the use of benzodiazepines for any presentation on a long-term basis